



(Pamidronate Disodium omega)

Ph.Eur.5.5 (Pamidronate Disodium Pentahydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in dichloromethane. It is sparingly soluble in dilute mineral acids and dissolves in dilute mineral acids and dissolves in dilute alkaline solutions. A 1.0% solution in water has a pH of 7.8 to 8.8.

USP 29 (Pamidronate Disodium). A white crystalline powder. Soluble in water and in 2N sodium hydroxide; sparingly soluble 0.1 N acetic acid and in 0.1 N hydrochloric acid; practically insoluble in organic solvents. PH of a 1% solution in water is between 7.8 and 8.8. Store in airtight containers at a temperature not exceeding 30 degrees.

Adverse Effects, Treatment, and Precautions

Fever and flu-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes) are common during intravenous infusion of pamidronate but generally resolve spontaneously. Pamidronate should not be given by bolus injection, as severe local reactions and thrombophlebitis have occurred. CNS effects include agitation, confusion, dizziness, lethargy, insomnia, and somnolence. There have been isolated cases of seizures, and visual hallucinations. In addition to hypocalcaemia and hypophosphataemia, which are common, hypomagnesaemia or hypokalaemia may occur, and rarely, hypernatraemia, or hyperkalaemia. Both hypotension and hypertension have been reported. Anaemia, thrombocytopenia, and lymphocytopenia may occur. Bronchospasm and interstitial pneumonitis have occurred rarely.

Pamidronate should be used with caution in those with cardiac disease, because of the potential for fluid overload, and in those who have had thyroid surgery, because of the increased risk of hypocalcaemia due to relative hypoparathyroidism. Serum electrolytes, calcium and phosphate should be monitored during therapy, along with renal function. Patients should be warned against driving or operating machinery after treatment if somnolence or dizziness occur.

Effects on the ears

Ototoxicity, manifest as tinnitus and sudden hearing loss, has been reported in 2 patients given both intravenous and oral pamidronate for pre-existing otosclerosis. A patient given 5 pamidronate infusions for Paget's disease developed tinnitus, vertigo, and hearing loss; the latter two resolved over 9 months, but tinnitus persisted².

Effect on electrolytes

Pamidronate has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in 2 patients. In each case, other conditions interfered with the expected compensatory physiological response to the hypocalcaemia.

Effects on the gastrointestinal tract

The tolerability of pamidronate given orally may depend to some extent on the particular formulation.

Gastrointestinal disturbances (in 21.8%) and haematological abnormalities (in 9.4%) were the main adverse effects associated with oral pamidronate in an open study of elderly patients. Oesophagitis, noted earlier in 4 of 49 patients given a different formulation, was not reported in this study.

Effects on the kidneys

Like other bisphosphonates, pamidronate may cause adverse renal effect. UK licensed product information notes that there have been isolated cases of haematuria, acute renal failure, and deterioration of pre-existing renal disease. Renal function should be monitored during long-term pamidronate therapy, especially in patients with pre-existing renal disease or a predisposition to renal impairment. Longer infusion times may reduce the risk of renal toxicity, and various infusion rates have been recommended, see uses and administration,

Effects on mental state

Palpitation, followed by visual hallucinations, suicidal ideation, and clinical depression were reported in an elderly man after a single infusion of pamidronate for Paget's disease; he had no previous psychiatric history. Treatment with thioridazine reduced the frequency and effect of the hallucination.

Effects on the musculoskeletal system

Although pamidronate appears to be a less potent inhibitor of bone mineralisation than etidronate, mineralisation defects have been reported in patients with paget's disease of bone receiving pamidronate. The resultant osteomalacia was not associated with any adverse clinical effects. Pamidronate –induced osteopetrosis has also been reported.² Acute pseudogout arthritis occurred in a woman treated with pamidronate for acute hypercalcaemia, possibly due to deposition of calcium in the joints. Severe bone pain occurred in more patients than expected when pamidronate was used for treatment of low bone density in cystic fibrosis; an increase in proinflammatory cytokines was postulated as a mechanism for this effect.

Osteonecrosis of the jaw has been reported after the use of pamidronate. The manufacturers have stated that the reported cases involved patients with cancer who also receiving chemotherapy and corticosteroids, and that most cases were associated with dental procedures such as tooth extraction; many patients had local infection

including osteomyelitis. for recommendations on dental care in patients prescribed intravenous bisphosphonates see.

Hypersensitivity

Allergic reaction to bisphosphonates are rare. Rash and pruritus occasionally follow pamidronate infusion. Mild skin rashes have also been reported in some patients taking pamidronate by mouth (see also under Bisphosphonates)

Interactions

As for the bisphosphonates in general,

Pharmacokinetics

plasma concentration of pamidronate rise rapidly after the start of an intravenous infusion; the apparent plasma half-life is 0.8hours. plasma protein binding about 54%. pamidronate is not metabolised, and about 20 to 55% of the dose is excreted in the urine unchanged within 72 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. renal clearance is slower in patients with severe renal impairment an infusion rates may need to be reduced.

Like all bisphosphonates, oral pamidronate is poorly absorbed from the gastrointestinal tract; bioavailability is about 1 to 3%.

Uses and administration

Pamidronate is an aminobisphosphonate with general properties similar to the other bisphosphonates. It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses.

Pamidronate is used as an adjunct in treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic lesions and bone pain in multiple myeloma or bone metastases associated with breast cancer. It may also be of benefit in bone disorders associated with excessive bone resorption, including Paget's disease of bone.

Pamidronate disodium is given by slow intravenous infusion. UK licensed product information recommends infusion at a rate not exceeding 60 mg/hour (or not exceeding 20 mg/hour in patients with established or suspected renal impairment) and at a concentration not exceeding 60 mg per 250 ml of infusion solution (sodium chloride 0.9% or glucose 5%). In the USA, the recommended concentration of infusion and rate vary depending on the indication.

In hypercalcaemia of malignancy, pamidronate disodium is given by slow intravenous infusion in a total dose of 15 to 90 mg according to the initial plasma-calcium concentration. In the UK, the total dose is given as a single infusion or in divided doses over 2 to 4 days. In the USA, the total dose is given as a single infusion, doses of 60 mg to 90 mg being given over 2 to 24 hours. Plasma-calcium concentrations generally start declining 24 to 48 hours after a dose of pamidronate with normalisation within 3 to 7 days. Treatment may be repeated if normocalcaemia is not achieved within this time or if hypercalcaemia recurs.

In patients with osteolytic lesions and bone pain of multiple myeloma or bone metastases associated with breast cancer, pamidronate disodium may be given in doses of 90 mg by intravenous infusion every 3 to 4 weeks.

In the treatment of Paget's disease the regimen in the UK is 30 mg by slow infusion once a week for 6 weeks (total dose 180 mg), or 30 mg in the first week then 60 mg every other week for 6 weeks (total dose 210 mg). These courses may be repeated every 6 months, and the total dose increased if necessary up to a maximum of 360 mg. Alternatively, the dose used in the USA is 30 mg by infusion over 4 hours, repeated on consecutive days to a total dose of 90 mg. This course is repeated when clinically indicated.

Pamidronate has also been given by mouth.

Administration in renal impairment

Pharmacokinetic studies suggest that no dosage reduction of pamidronate disodium is required in patients with any degree of renal impairment. However, UK product information currently recommended that the rate of infusion be reduced to a maximum of 20 mg/hour for patient with established or suspected renal impairment; use in those with severe renal impairment (creatinine clearance less than 30 ml/minute) is not advised as clinical experience is limited.

Gaucher disease

Treatment with oral pamidronate disodium in doses of 600 mg daily in adults,¹ and 150 to 300 mg daily in children, or intravenous pamidronate disodium in doses of 45 mg every 3 weeks, has been reported to improve bone lesions of Gaucher disease in a few patients.

Hypercalcaemia

Bisphosphonates, of which pamidronate is one of the most effective, are the preferred drug for treating hypercalcaemia of malignancy once the patient has been adequately rehydrated.

Malignant neoplasms of the bone

Bisphosphonates are of benefit in some patients with metastatic bone disease not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Pamidronate is licensed for such use in many countries. A literature review of phase II and III studies concluded that pamidronate was effective in the treatment of pain and skeletal complication from metastatic disease, particularly in patients with breast cancer or multiple myeloma, but that its efficacy in those with other neoplasms needed confirmation.

A long-term follow-up of 2 randomised trials of pamidronate in women with breast cancer confirmed its efficacy over placebo. However, a pooled analysis of its use for palliation of bone pain in men metastatic prostate cancer found no treatment benefit

with pamidronate over placebo. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

Osteogenesis imperfecta

Pamidronate has produced benefit in patients with osteogenesis imperfecta. Although the dosage and timing varied between centres and age groups, all patients were given cyclical intravenous pamidronate; bone mineral density increased, fracture incidence decreased, and patients reported improvements in mobility, pain and chronic fatigue, while bone size and density also increased in patients given pamidronate, especially in those with larger baseline deficits in bone mass, serum calcium decreased markedly, and bone turnover was suppressed; clinical problems were not evident if calcium intake was sufficient, but consequences of a chronically low bone turnover are unknown.

Osteoporosis

Bisphosphonates are used in the prevention and treatment of osteoporosis. A placebo-controlled trial of oral pamidronate 150 mg daily found it to be effective in increasing bone mineral density (BMD) of the lumbar spine and femoral neck in both men and women. Intravenous pamidronate at 30 mg every 3 months, or 60 mg every 6 months, also increased BMD in the lumbar spine, femoral neck, and trochanter in an observational, retrospective study. Single intravenous infusions of pamidronate given every 3 months have also been reported to increase BMD and reduce fracture rates in children with osteoporosis; annual doses were in the region of 4 mg/kg.

In a small study⁵ of patients receiving corticosteroids, pamidronate given intravenously either as a single infusion of 90 mg, or as 90 mg followed by 30 mg every 3 months for 1 year, significantly increased BMD at the lumbar spine, femoral neck, and total hip. In lymphoma patients receiving corticosteroids as part of chemotherapy regimens, pamidronate 30 mg intravenously every 3 months reduced bone loss when compared with placebo. Pamidronate has shown beneficial increases in or preservation of BMD in patients after heart, liver, or lung transplantation.

An open study in men with prostate cancer (but no metastases) and receiving leuprolide, found that addition of pamidronate 60 mg intravenously every 12 weeks prevented bone loss in the hip and lumbar spine.

Acute bone loss from the femur and pelvis after hip arthroplasty was also reduced by a single infusion of 90 mg pamidronate in a small prospective study.¹¹

Paget's disease of bone

Bisphosphonates may be indicated for patients with Paget's disease of bone ,if bone pain is persistent , or to prevent further progression of the disease. Pamidronate was initially used orally for paget's disease , but intravenous therapy has been preferred because of a lower incidence of adverse effects. with the usual total dose of 180 mg , remission is considered likely in most patients with mild to moderate disease , but unlikely if disease is severe . However ,high doses (about 340 mg) were found to be effective in those with very active disease , and also associated with a longer remission . in a 2-year study of 3 different doses , pamidronate increased bone

mineral density in pagetic bone of the lumbar spine ,femoral neck ,and total hip , but lacked this effect on non-pagetic bone in the same areas; loss of density was apparent in non-pagetic forearm bone in the group receiving the highest dose (240 mg).patients with co-existent osteoarthritis or arthropathy responded less well to pamidronate in terms of pain perception, than those patients without joint disease. while hearing loss may not improve with pamidronate , there has been a report of successful treatment of optic neuropathy due to paget's disease with pamidronate and dexamethasone.⁶ bisphosphonates have also been given in other bone diseases with a similar pathology ,particularly increased osteoclastic resorption .For example ,pamidronate has had beneficial effects in patients with fibrous dysplasia of bone ,a rare congenital disease leading to osteolytic lesions.

Rheumatoid arthritis and spondyloarthropathis

Intravenous and oral administration of pamidronate has reportedly produced some modification of disease in a few patients with rheumatoid arthritis. Continuous oral pamidronate therapy was shown to be effective in preserving and increasing bone mass in a 3-year randomised controlled trial involving 105 patients with rheumatoid arthritis. In contrast , a small controlled trial in 26 patients found no significant effect on rheumatoid arthritis disease activity with intravenous pamidronate . There are reports of an analgesic response to pamidronate in patients with acute rheumatic pain of various aetiologies , including arthritis and ankylosing spondylitis, and a trial in patients with ankylosing spondylitis found a dose-dependent therapeutic effect with pamidronate.

Packaging

10-ml vial ,Latex-free stopper ,White Flip-off cap

10-ml vial , Latex-free stopper ,Green Flip-off cap

10-ml vial , Latex-free stopper ,Blue Flip-off cap

Storage condition

Store between 15 and 25°C.

Do not freeze.